(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 478 001 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
12.06.1996 Bulletin 1996/24

(21) Application number: **91119345.6**

(22) Date of filing: **17.03.1987**

(51) Int. Cl.[6]: **C07C 251/60**, C07C 255/62, C07D 257/04, C07D 207/46, C07D 339/08, A61K 31/15

(54) Benzophenone oxime derivatives, pharmaceutical compositions and use

Benzophenon Oxim Derivate, pharmaceutische Zusammensetzungen und ihre Verwendung

Dérivés de benzophénone oxime, compositions pharmaceutiques et leur utilisation

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(30) Priority: **17.03.1986 JP 57061/86**
26.03.1986 JP 65963/86

(43) Date of publication of application:
01.04.1992 Bulletin 1992/14

(62) Application number of the earlier application in accordance with Art. 76 EPC: **87103834.5**

(73) Proprietor: **Eisai Co., Ltd.**
Tokyo (JP)

(72) Inventors:
- **Yamagishi, Youji**
  Niihari-gun, Ibaraki (JP)
- **Akasaka, Kozo**
  Ushiku-shi, Ibaraki (JP)
- **Suzuki, Takeshi**
  Ushiku-shi, Ibaraki (JP)
- **Miyamoto, Mitsuaki**
  Tsuchiura-shi, Ibaraki (JP)
- **Nakamoto, Kouji**
  Kawaguchi-shi, Saitama (JP)
- **Okano, Kazuo**
  Yatabemachi, Tsukuba-gun, Ibaraki (JP)
- **Abe, Shinya**
  Ushiku-shi, Ibaraki (JP)
- **Ikuta, Hironori**
  Ushiku-shi, Ibaraki (JP)
- **Hayashi, Kenji**
  Tsukuba-shi, Ibaraki (JP)
- **Yoshimura, Hiroyuki**
  Yatabemachi, Tsukuba-gun, Ibaraki (JP)
- **Fujimori, Tohru**
  Tsukuba-gun, Ibaraki (JP)
- **Harada, Koukichi**
  Yatabemachi, Tsukuba-gun, Ibaraki (JP)
- **Yamatsu, Isao**
  Ushiku-shi, Ibaraki (JP)

(74) Representative: **Hansen, Bernd, Dr.rer.nat. et al**
Hoffmann, Eitle & Partner
Patentanwälte
Postfach 81 04 20
81904 München (DE)

(56) References cited:
FR-A- 2 385 691

EP 0 478 001 B1

Description

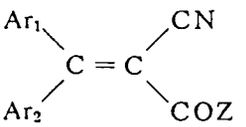
The invention relates to diphenylethylene derivatives, a process for preparing the same and the pharmaceutical use thereof.

The most serious diseases for mankind at present include acute vascular diseases such as myocardial infarction, cerebral apoplexy, cerebral thrombosis, cerebral infarction, pulmonary embolus, deep phlebothrombosis and peripheral arteriothrombosis.

Recently antiplatelet agents have attracted public attention and been clinically employed for treating these diseases. However their application has been only lately realized. Thus it is expected to develop better drugs in future.

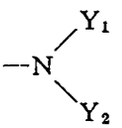
GB-999,613 includes diphenyl acrylic acid derivatives being useful to impart to organic materials superior resistance to degradation and deterioration when they are exposed to ultraviolet radiation. The above document is especially concerned with α-cyano-β,β-diphenyl acrylic acid derivatives.

CH-455,676 refers to the use of compounds of the formula (I):



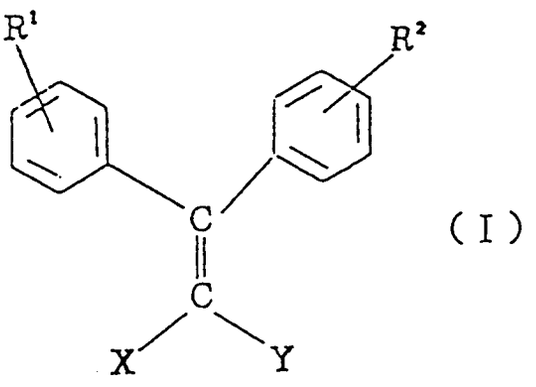
(I)

wherein Ar_1 and Ar_2 represent aromatic carbocyclic residues not including primary, secondary or tertiary amino groups as substituents, and wherein Z is represented by -OY or



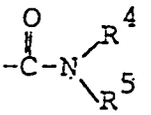
wherein Y, Y_1 and Y_2 are hydrogen atoms or organic residues, for the protection of non-textile, organic materials against ultraviolet radiation.

The present invention provides a diphenylethylene derivative of the general formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein R^1 and R^2 may be the same or different from each other and each represents hydrogen, hydroxyl or a C_1-C_6 alkoxy group; X represents a cyano group; and Y represents a group of the formula

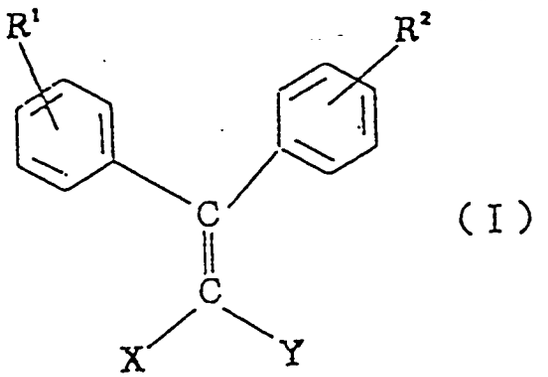


(wherein R^4 and R^5 may be the same or different from each other and each represents a group selected from benzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, phenethyl, 2-picolyl, 3-picolyl and 4-picolyl); or a group of the formula $-CH_2-NHSO_2-C_6H_5$ or $-C(R^8)=NR^7$, R^7 being a C_1-C_6 alkoxy or an aryl, R^8 is $-VR^9$, V being oxygen, sulfur or nitrogen, R^9 being an alkyl or an aryl, or a pharmaceutically acceptable salt thereof.

In the above definition, a C_1-C_6 alkyl group as mentioned with regard to R^4 and R^5 includes straight-chain or branched alkyl groups carrying one to six carbon atoms, e.g. methyl, ethyl, n-propyl, n-butyl, isopropyl, isobutyl, 1-methylpropyl, tert-butyl, n-pentyl, 1-ethylpropyl, isoamyl and n-hexyl groups. An alkoxy group as mentioned with regard to R^1 and R^2 includes any lower alkoxy group derived from the lower alkyl groups as cited above. Among these groups, methyl and ethyl groups are the most desirable lower alkyl groups while a methoxy group is the most desirable lower alkoxy group.

In addition, the invention provides a plurality of processes for preparing the above defined diphenylethylene derivative. Each process is explained below in detail.

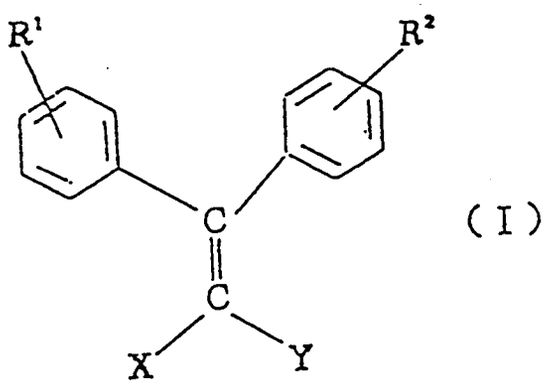
Moreover the invention provides a pharmaceutical composition which comprises a pharmacologically effective amount of a diphenylethylene derivative of the formula:



(I)

wherein R^1 and R^2 are independently from each other hydrogen, hydroxyl or a C_1-C_6 alkoxy group, X is cyano, Y is $-CO-NR^4R^5$, R^4 and R^5 each being hydrogen, a C_1-C_6 alkyl or a group selected from benzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, phenethyl, 2-picolyl, 3-picolyl and 4-picolyl; $-CH_2-NHSO_2-C_6H_5$ or $-C(R^8)=NR^7$, R^7 being a C_1-C_6 alkoxy or an aryl, R^8 is $-VR^9$, V being oxygen, sulfur or nitrogen, R^9 being an alkyl or an aryl,
or a pharmaceutically acceptable salt thereof,
and a pharmacologically acceptable carrier.

The invention also provides the use of a diphenylethylene derivative of the formula:



(I)

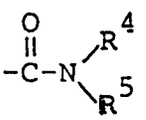
wherein R^1 and R^2 are independently from each other hydrogen, hydroxyl or a C_1-C_6 alkoxy group, X is cyano, Y is -CO-NR^4R^5, R^4 and R^5 each being hydrogen, a C_1-C_6 alkyl or a group selected from benzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, phenethyl, 2-picolyl, 3-picolyl and 4-picolyl; -CH_2-$NHSO_2$-C_6H_5 or -$C(R^8)$=NR^7, R^7 being a C_1-C_6 alkoxy or an aryl, R^8 is -VR^9, V being oxygen, sulfur or nitrogen, R^9 being an alkyl or an aryl, or a pharmaceutically acceptable salt thereof,
in the preparation of a medicament for the treatment of diseases caused by blood stream disorders.

The invention compound will be explained in more detail in line with the above shown embodiments.

Process for Preparation

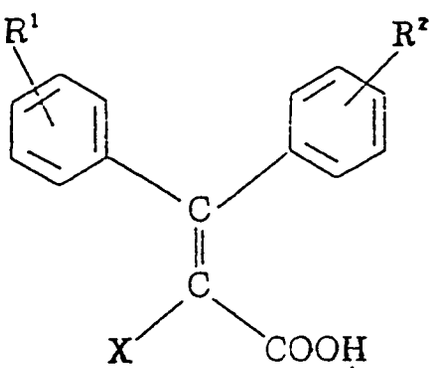
There may be various processes for preparing the compound (I) of the present invention. Typical examples thereof are as follows.

(1) The aimed compound of the formula (I), wherein Y is a group of the formula



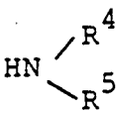
(wherein R^4 and R^5 are as defined above).

A carboxylic acid of the general formula (II):



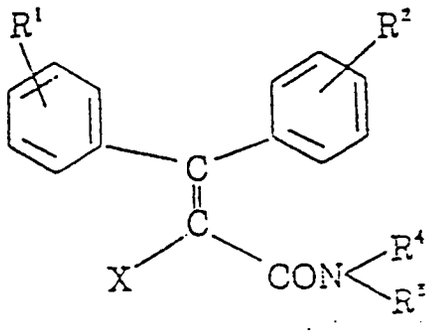
(II)

wherein R^1, R^2 and X are as defined above, or a reactive acid derivative thereof is converted into an amide by reacting with an amine of the general formula:



(III)

wherein R^4 and R^5 are as defined above,
to give a compound (I') which is one of the aimed compounds of the present invention:



(I')

wherein R^1, R^2, X, R^4 and R^5 are as defined above.

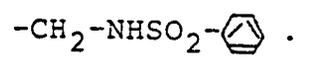
A reactive acid derivative of the compound (III) includes, for example, a halide, an anhydride or a mixture of acid anhydrides of the compound (III). This reaction may be carried out in the presence of dehydrating agent(s) such as N,N'=dicyclohexylcarbodiimide, N,N'-diethylcarbodiimide, trialkyl phosphates, polyphosphate or tosyl chloride, if required.

When a halide is used as a reactive derivative, base(s) may be added to the reaction mixture to bind the hydrogen halide formed during the reaction, thus accelerating the reaction. Examples of the bases are inorganic salts such as potassium hydroxide, sodium hydroxide, potassium carbonate and sodium carbonate and tertiary amines such as pyridine and triethylamine.

This reaction may be usually carried out in a solvent. Any solvent may be employed so long as it exhibits no adverse effect on the reaction. Examples of such a solvent are dimethyl sulfoxide, tetrahydrofuran, dioxane, ethanol and mixtures thereof.

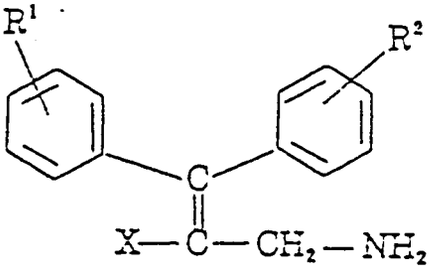
The reaction may be usually carried out at a temperature of -50 to 200°C unless particularly limited. After the completion of the reaction, the aimed compound may be isolated in a conventional manner.

(2) The aimed compound of the formula (I), wherein Y is a group of the formula



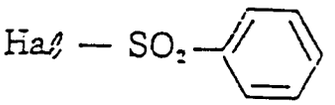
.

An amine of the general formula (IV):



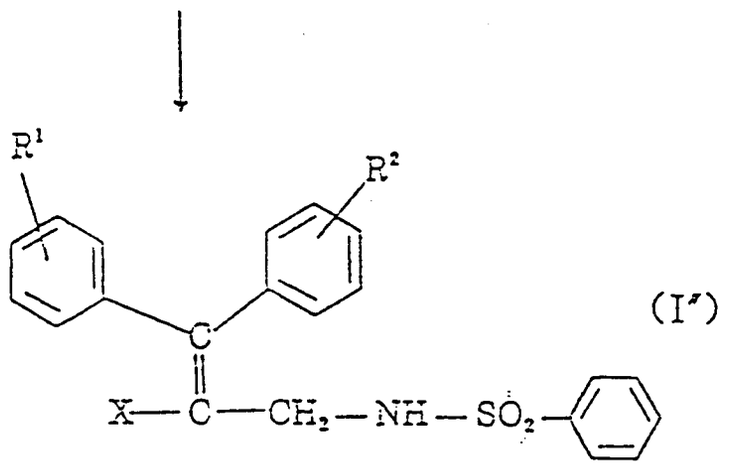
(IV)

wherein R^1, R^2 and X are as defined above,
is reacted with a sulfonyl halide of the general formula (V):



(V)

wherein Hal represents a halogen atom,
in a conventional manner to thereby readily give the aimed compound (I") in the form of a sulfonamide:



(I")

This reaction may be usually carried out in a solvent. Any solvent may be employed so long as it exhibits no adverse effect on the reaction. Examples of such a solvent are chloroform, 1,2-dichloroethane, ethyl ether, pyridine, tetrahydrofuran, dioxane, ethylene glycol dimethyl ether, benzene, toluene and mixtures thereof.

The temperature at which this reaction is carried out is not particularly limited. Usually a temperature of -50 to 150°C is preferable. After the completion of the reaction, the aimed compound may be isolated in a conventional manner.

The invention compound is defined to include a compound having the formula (I) in which Y is $-C(R^8)=NR^7$, that is, $-C(VR^9)=NR^7$, R^7 being a C_1-C_6 alkoxy or an aryl, V being oxygen, sulfur or nitrogen, R^9 being an alkyl or an aryl.

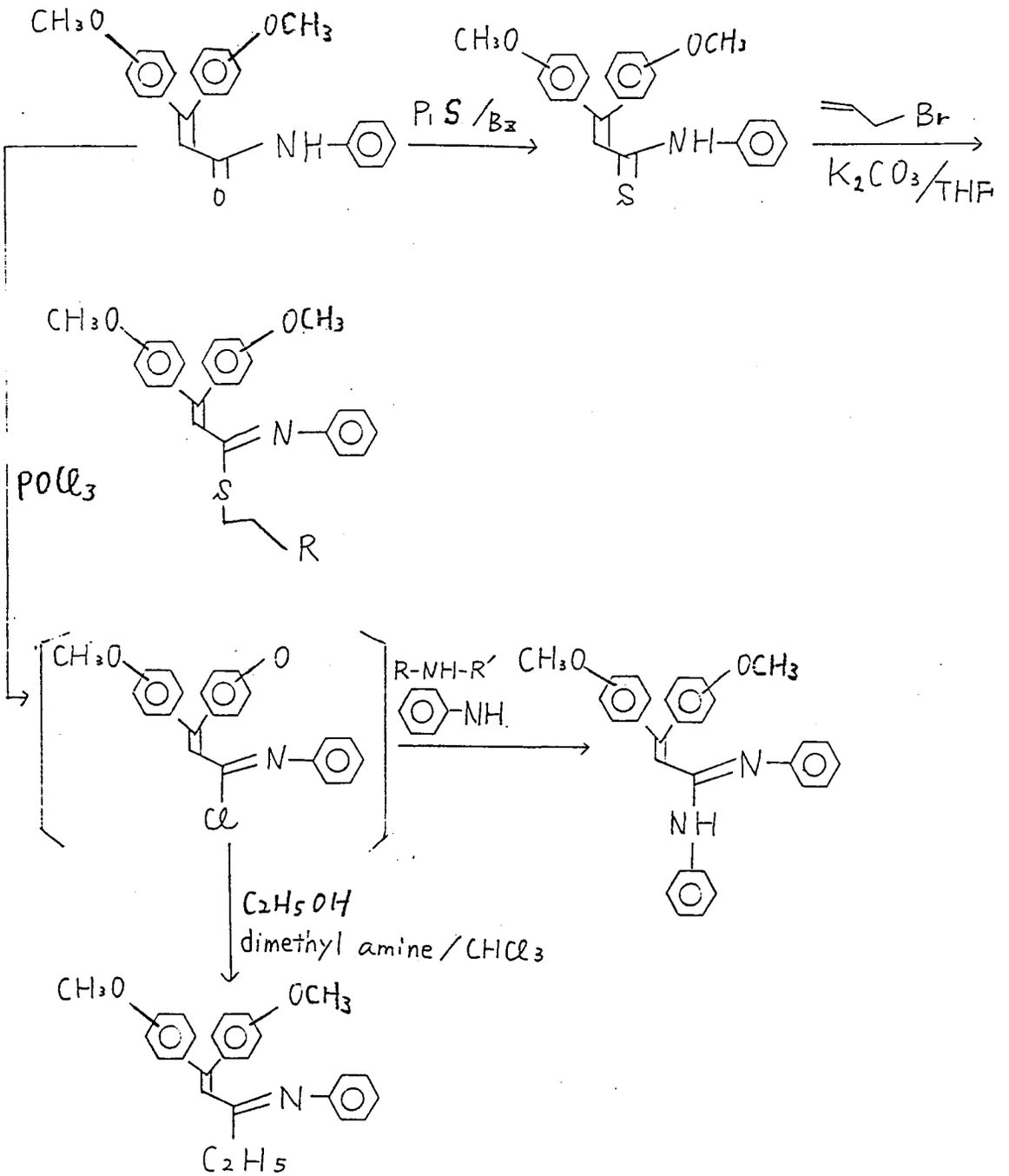
The compound is prepared by the below given procedures.

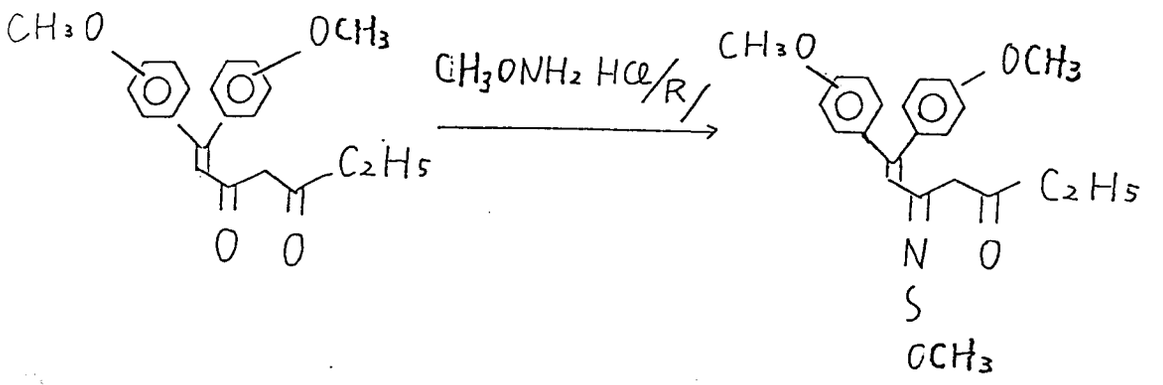
(3) A compound having the formula (I) in which Y is $-CONHR^7$ is reacted with a compound having the formula of HVR^9 by a halogenating agent such as phosphorus oxychloride, phosphorus pentachloride and thionyl chloride to obtain a compound having the formula (I) in which Y is $-C(VR^9)=NR^7$, in a solvent such as benzene, toluene and chloroform. The reaction may be effected in the presence of an organic base such as dimethylaniline, triethylamine and pyridine or an inorganic base such as potassium carbonate and sodium carbonate.

(4) The same starting compound as used in the preparation (3) is reacted with a sulfurizing agent such as phosphorus pentasulfide in a solvent such as benzene and toluene to obtain a corresponding thioamide having the formula (I) in which Y is -C(=S)-NH-R^7. Then the thioamide is reacted with a halide having the formula of R^9-hal to obtain a compound having the formula (I) in which Y is -C(SR^9)=NR^7. A solvent and. a base may be used in the same was as shown in the preparation (3).

(5) A compound having the formula (I) in which Y is -C(VR^9)=NR^7, R^9 is an alkyl and R^7 is a C_1-C_6 alkoxy is obtained below. A compound having the formula (I) in which Y is -CO-VR^9 is reacted with H_2N-R^7 to obtain the above intended compound.

The above shown procedures are illustrated below.





The diphenyl ethylene derivative of the invention exhibits an excellent effect in the pharmacological point of view. It effectively inhibits the agglutination of platelets and eventually is useful for a remedy of an antiplatelet and antithrombotic agent. In particular, it is useful for treating and/or preventing cerebrovascular diseases such as transient ischemic attack (TIA), cerebral infarction (thrombus and embolus) and cerebral arteriosclerosis; postoperative thrombus, embolus and blood stream disorders accompanying vascular operation and extracorporeal circulation; chronic arterial obstructions such as Buerger's disease, obstructive arteriosclerosis, peripheral arteriosclerosis, SLE and Raynaud's disease; and ischemic cardial diseases such as stenocardia and myocardial infarction. It is further useful for preventing recurrence of these diseases and for improving prognosis thereof.

When the compound of the present invention is used as an antiplatelet and antithrombotic agent, it may be orally or parenterally, for example, intramuscularly, subcutaneously or intravenously administered. The dose thereof may vary depending on, for example, the disease, the condition and the age of each patient. Unless particularly limited, it may be administered in a dose of 0.1 to 300 mg, preferably 0.1 to 60 mg, particularly preferably 0.3 to 30 mg, further particularly preferably 0.6 to 10 mg to an adult per day.

The compound of the present invention may be formulated into, for example, tablets, granules, powders, capsules, injections or suppositories in conventional manners known in the art.

When it is to be formulated into solid preparations for oral administration, excipients and, if required, other additives such as binders, disintegrants, lubricants, colorants and corrigents are added to the base and the obtained mixture is then formulated into, for example, tablets, coated tablets, granules, powders or capsules in conventional manners.

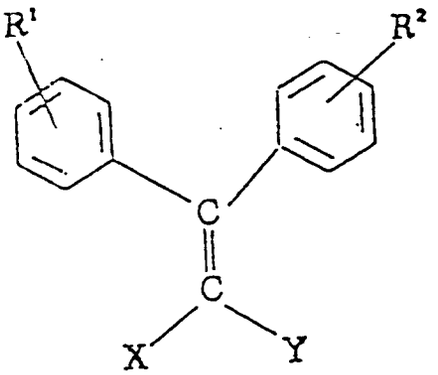
Examples of the excipients are lactose, corn starch, white sugar, glucose, sorbitol and crystalline cellulose. Examples of the binders are polyvinyl alcohol, polyvinyl ether, ethylcellulose, methylcellulose, gum arabic, tragacanth, gelatin, shellac, hydroxypropylcellulose, hydroxypropylstarch and polyvinylpyrrolidone Examples of the disintegrants are starch, agar, powdery gelatin, crystalline cellulose, calcium carbonate, calcium hydrogencarbonate, calcium citrate, dextrin and pectin. Examples of the lubricants are magnesium stearate, talc, polyethylene glycol, silica and hardened vegetable oils. Examples of the colorants are those approved as additives for drugs. Examples of the corrigents are cocoa powder, methol, aromatic acids, peppermint oil, Borneo camphor and cinnamon powder. These tablets and granules may be, as a matter of course, coated with, for example, sugar or gelatin if required.

When an injection is to be prepared, various additives such as pH adjustors, buffers, stabilizers and preservatives are added to the base and the obtained mixture is formulated into an injection for subcutaneous, intramuscular or intravenous administration.

Claims

Claims for the following Contrating States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A pharmaceutical composition which comprises a pharmacologically effective amount of a diphenyl ethylene derivative of the formula;



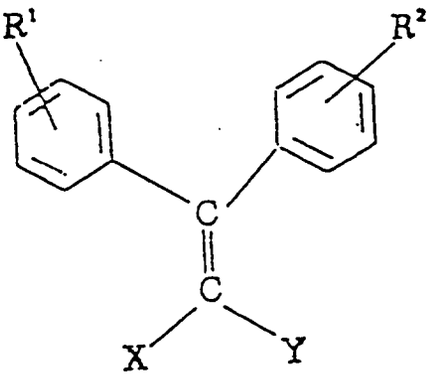
(I)

wherein R^1 and R^2 are independently from each other hydrogen, hydroxyl or a C_1-C_6 alkoxy group, X is cyano, Y is -CO-NR^4R^5, R^4 and R^5 each being hydrogen, a C_1-C_6 alkyl or a group selected from benzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, phenethyl, 2-picolyl, 3-picolyl and 4-picolyl; -CH_2-$NHSO_2$-C_6H_5 or -C(R^8)=NR^7, R^7 being a C_1-C_6 alkoxy or an aryl, R^8 is -VR^9, V being oxygen, sulfur or nitrogen, R^9 being an alkyl or an aryl,
or a pharmaceutically acceptable salt thereof,
and a pharmacologically acceptable carrier.

2. A pharmaceutical composition as claimed in claim 1, wherein in the formula (I) both of R^1 and R^2 are C_1-C_6 alkoxy groups.

3. A pharmaceutical composition as claimed in claim 2, wherein in the formula (I) both of R^1 and R^2 are methoxy groups.

4. Use of a diphenyl ethylene derivative of the formula:



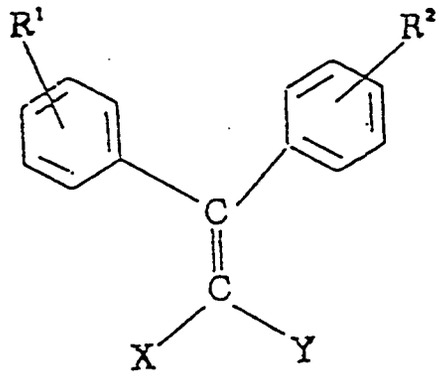
(I)

wherein R^1 and R^2 are independently from each other hydrogen, hydroxyl or a C_1-C_6 alkoxy group, X is cyano, Y is -CO-NR^4R^5, R^4 and R^5 each being hydrogen, a C_1-C_6 alkyl or a group selected from benzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, phenethyl, 2-picolyl, 3-picolyl and 4-picolyl; -CH_2-$NHSO_2$-C_6H_5 or -C(R^8)=NR^7, R^7 being a C_1-C_6 alkoxy or an aryl, R^8 is -VR^9, V being oxygen, sulfur or nitrogen, R^9 being an alkyl or an aryl,
or a pharmaceutically acceptable salt thereof,
in the preparation of a medicament for the treatment of diseases caused by blood stream disorders.

5. The use as claimed in claim 4, wherein in the formula (I) both of R^1 and R^2 are C_1-C_6 alkoxy groups.

6. The use as claimed in claim 5, wherein in the formula (I) both of R^1 and R^2 are methoxy groups.

7. A diphenyl ethylene derivative of the formula:



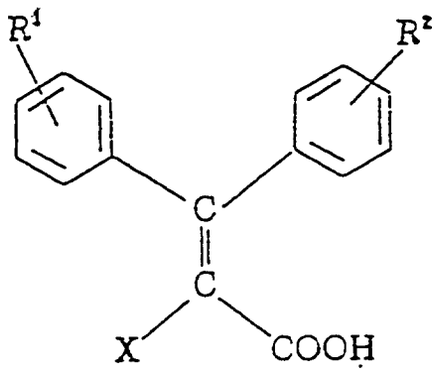
(I)

wherein R^1 and R^2 are independently from each other hydrogen, hydroxyl or a C_1-C_6 alkoxy group, X is cyano, Y is -CO-NR^4R^5, R^4 and R^5 each being a group selected from benzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, phenethyl, 2-picolyl, 3-picolyl and 4-picolyl; -CH_2-$NHSO_2$-C_6H_5 or -$C(R^8)$=NR^7, R^7 being a C_1-C_6 alkoxy or an aryl, R^8 is -VR^9, V being oxygen, sulfur or nitrogen, R^9 being an alkyl or an aryl,
or a pharmaceutically acceptable salt thereof.

8. A diphenyl ethylene derivative as claimed in claim 7, wherein both of R^1 and R^2 are C_1-C_6 alkoxy groups, or a pharmaceutically acceptable salt thereof.

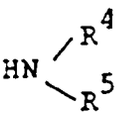
9. A diphenyl ethylene derivative as claimed in claim 8, wherein both of R^1 and R^2 are methoxy groups, or a pharmaceutically acceptable salt thereof.

10. A process for preparing a diphenyl ethylene derivative of the general formula (I) as given by claim 7, wherein R^1, R^2 and X are as defined above, Y is -CO-NR^4R^5, R^4 and R^5 are each as defined above, or a pharmaceutically acceptable salt thereof, which comprises reacting a carboxylic acid of the general formula (II):



(II)

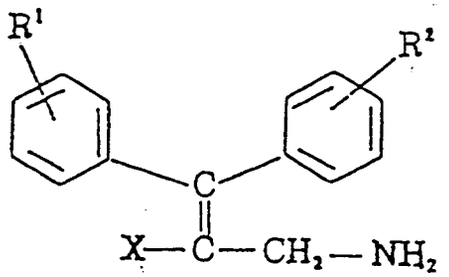
wherein R^1, R^2 and X are as defined above, or a reactive acid derivative thereof with an amine of the general formula (III):



(III)

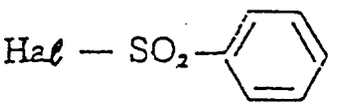
wherein R^4 and R^5 are as defined above, and if necessary, converting the product to a pharmaceutically acceptable salt.

11. A process for preparing a diphenyl ethylene derivative of the general formula (I) as given by claim 7, wherein R^1, R^2 and X are as defined above, Y is $-CH_2NHSO_2-C_6H_5$, or a pharmaceutically acceptable salt thereof, which comprises reacting an amine of the general formula (IV):



(IV)

wherein R^1, R^2 and X are as defined above with a sulfonyl halide of the general formula (V):



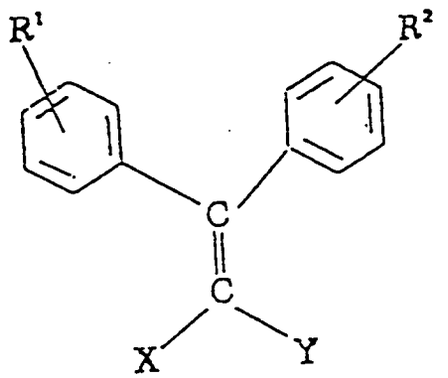
(V)

wherein Hal represents a halogen atom, and if necessary, converting the product to a pharmaceutically acceptable salt.

12. A process for preparing a diphenyl ethylene derivative of the general formula (I) as given by claim 7, wherein R^1, R^2 and X are as defined above, Y is $-C(R^8)=NR^7$, R^7, R^8, V and R^9 being as defined above, or a pharmaceutically acceptable salt thereof, which comprises reacting a compound of the general formula (I) as given by claim 7 wherein R^1, R^2 and X are as defined above and Y is $-CONHR^7$, R^7 being a C_1-C_6 alkoxy or an aryl, with a compound of the formula HVR^9, wherein V and R^9 are as defined above, in the presence of a halogenating agent and, if necessary, converting the product to a pharmacaeutically acceptable salt thereof.

Claims for the following Contracting States : AT, ES, GR

1. Use of a diphenyl ethylene derivative of the formula:



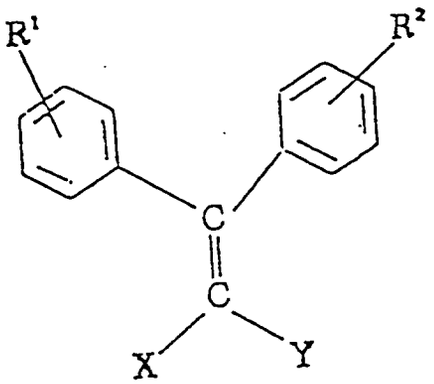
(I)

wherein R^1 and R^2 are independently from each other hydrogen, hydroxyl or a C_1-C_6 alkoxy group, X is cyano, Y is -CO-NR^4R^5, R^4 and R^5 each being hydrogen, a C_1-C_6 alkyl or a group selected from benzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, phenethyl, 2-picolyl, 3-picolyl and 4-picolyl; -CH_2-$NHSO_2$-C_6H_5 or -$C(R^8)=NR^7$, R^7 being a C_1-C_6 alkoxy or an aryl, R^8 is -VR^9, V being oxygen, sulfur or nitrogen, R^9 being an alkyl or an aryl,
or a pharmaceutically acceptable salt thereof,
in the preparation of a medicament for the treatment of diseases caused by blood stream disorders.

2. The use as claimed in claim 1, wherein in the formula (I) both of R^1 and R^2 are C_1-C_6 alkoxy groups.

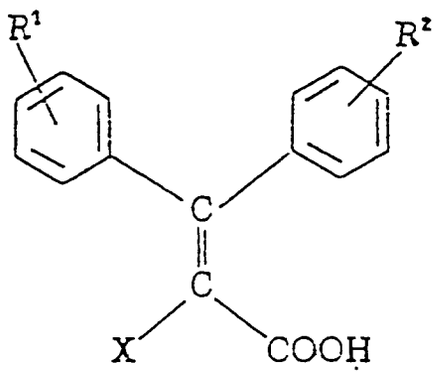
3. The use as claimed in claim 2, wherein in the formula (I) both of R^1 and R^2 are methoxy groups.

4. A process for preparing a diphenyl ethylene derivative with the formula (I):



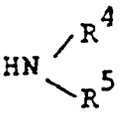
(I)

wherein R^1 and R^2 are independently from each other hydrogen, hydroxyl or a C_1-C_6 alkoxy group, X is cyano, Y is -CO-NR^4R^5, R^4 and R^5 each being a group selected from benzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, phenethyl, 2-picolyl, 3-picolyl and 4-picolyl, or a pharmaceutically acceptable salt thereof, which comprises reacting a carboxylic acid of the general formula (II):



(II)

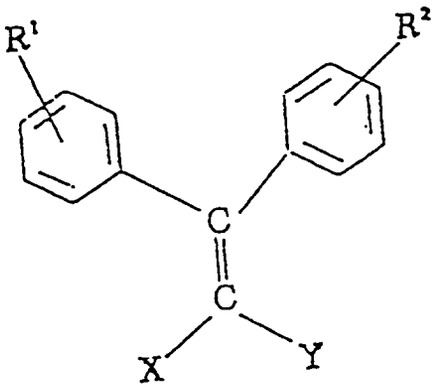
wherein R^1, R^2 and X are as defined above, or a reactive acid derivative thereof with an amine of the general formula (III):



(III)

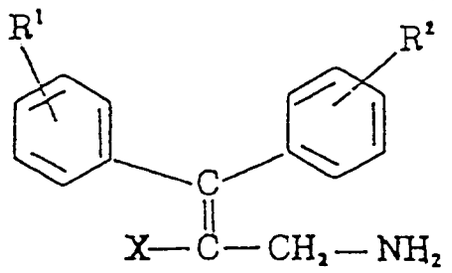
wherein R^4 and R^5 are as defined above, and if necessary, converting the product to a pharmaceutically acceptable salt.

5. A process for preparing a diphenyl ethylene derivative of the formula (I):



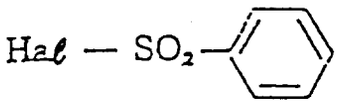
(I)

wherein R^1 and R^2 are independently from each other hydrogen, hydroxyl or a C_1-C_6 alkoxy group, X is cyano, Y is $-CH_2-NHSO_2-C_6H_5$, or a pharmaceutically acceptable salt thereof, which comprises reacting an amine of the general formula (IV):



(IV)

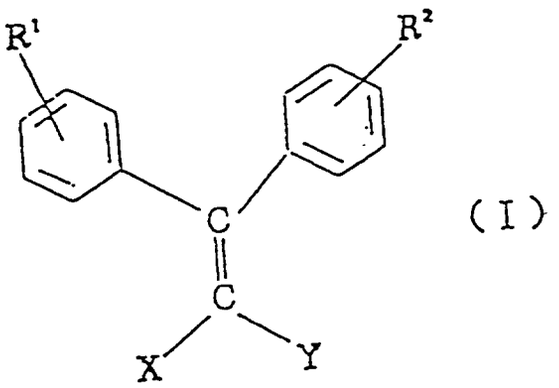
wherein R^1, R^2 and X are as defined above, with a sulfonyl halide of the general formula (V):



(V)

wherein Hal represents a halogen atom, and if necessary, converting the product to a pharmaceutically acceptable salt.

6. A process for preparing a diphenyl ethylene derivative of the formula (I):



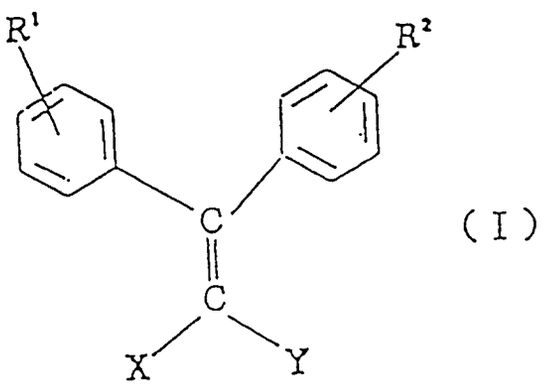
(I)

wherein R^1 and R^2 are independently from each other hydrogen, hydroxyl or a C_1-C_6 alkoxy group, X is cyano, Y is -C(R^8)=NR^7, R^7 being a C_1-C_6 alkoxy or an aryl, R^8 is -VR^9, V being oxygen, sulfur or nitrogen, R^9 being an alkyl or an aryl, or a pharmaceutically acceptable salt thereof, which comprises reacting a compound of the general formula (I) as given above, wherein R^1, R^2 and X are as defined above and Y is -CONHR^7, R^7 being a C_1-C_6 alkoxy or an aryl, with a compound of the formula HVR^9, wherein V and R^9 are as defined above, in the presence of a halogenating agent and, if necessary, converting the product to a pharmaceutically acceptable salt thereof.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Pharmazeutische Zusammensetzung, umfassend eine pharmakologisch effektive Menge eines Diphenylethylen-Derivates der Formel:



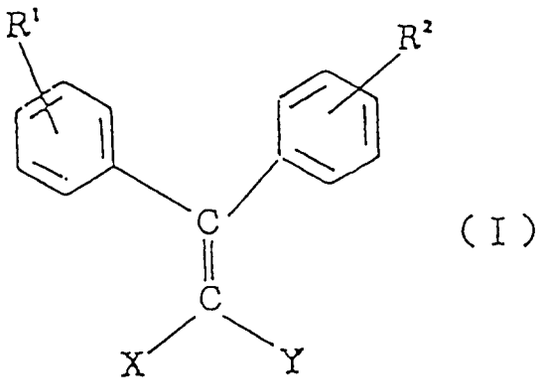
(I)

worin R^1 und R^2 unabhängig voneinander jeweils Wasserstoff, Hydroxyl- oder eine C_1-C_6-Alkoxy-Gruppe, X Cyano, Y -CO-NR^4R^5, worin R^4 und R^5 jeweils Wasserstoff, ein C_1-C_6-Alkyl oder eine Gruppe bedeuten, ausgewählt aus Benzyl, 2-Chlorbenzyl, 3-Chlorbenzyl, 4-Chlorbenzyl, 2-Methylbenzyl, 3-Methylbenzyl, 4-Methylbenzyl, 2-Methoxybenzyl, 3-Methoxybenzyl, 4-Methoxybenzyl, Phenethyl, 2-Picolyl, 3-Picolyl und 4-Picolyl; -CH_2-NHSO_2-C_6H_5 oder -C(R^8)=NR^7 sind, worin R^7 ein C_1-C_6-Alkoxy oder ein Aryl, R^8 -VR^9 sind, worin V Sauerstoff, Schwefel oder Stickstoff, R^9 ein Alkyl oder Aryl sind, oder ein pharmazeutisch akzeptables Salz davon und einen pharmakologisch akzeptablen Träger.

2. Pharmazeutische Zusammensetzung nach Anspruch 1, worin in der Formel (I) R^1 und R^2 jeweils C_1-C_6-Alkoxy-Gruppen sind.

3. Pharmazeutische Zusammensetzung nach Anspruch 2, worin in der Formel (I) R^1 und R^2 jeweils Methoxy-Gruppen sind.

4. Verwendung eines Diphenylethylen-Derivates der Formel



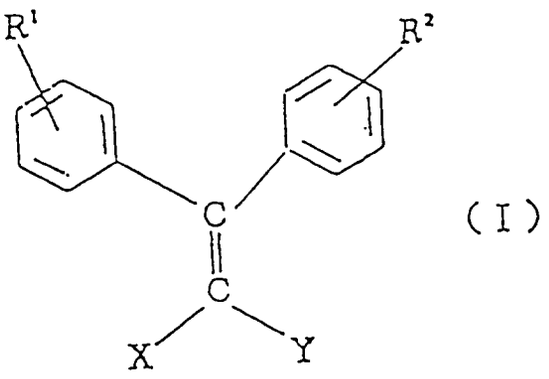
(I)

worin R^1 und R^2 unabhängig voneinander jeweils Wasserstoff, Hydroxyl- oder eine C_1-C_6-Alkoxy-Gruppe, X Cyano, Y -CO-NR^4R^5, worin R^4 und R^5 jeweils Wasserstoff, ein C_1-C_6-Alkyl oder eine Gruppe bedeuten, ausgewählt aus Benzyl, 2-Chlorbenzyl, 3-Chlorbenzyl, 4-Chlorbenzyl, 2-Methylbenzyl, 3-Methylbenzyl, 4-Methylbenzyl, 2-Methoxybenzyl, 3-Methoxybenzyl, 4-Methoxybenzyl, Phenethyl, 2-Picolyl, 3-Picolyl und 4-Picolyl; $-CH_2-NHSO_2-C_6H_5$ oder $-C(R^8)=NR^7$ sind, worin R^7 ein C_1-C_6-Alkoxy oder ein Aryl, R^8 -VR^9 sind, worin V Sauerstoff, Schwefel oder Stickstoff, R^9 ein Alkyl oder Aryl sind, oder eines pharmazeutisch akzeptablen Salzes davon zur Herstellung eines Medikamentes für die Behandlung von Erkrankungen, die durch Blutstromstörungen verursacht werden.

5. Verwendung nach Anspruch 4, worin in der Formel (I) R^1 und R^2 jeweils C_1-C_6-Alkoxy-Gruppen sind.

6. Verwendung nach Anspruch 5, worin der Formel (I) R^1 und R^2 Methoxy-Gruppen sind.

7. Diphenylethylen-Derivat der Formel:



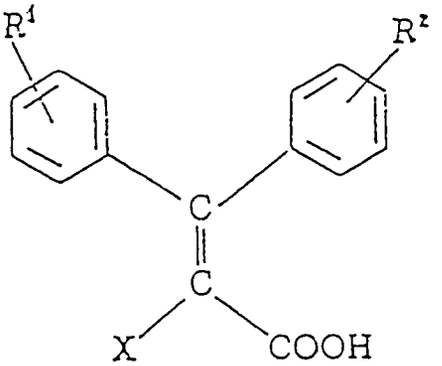
(I)

worin R^1 und R^2 unabhängig voneinander jeweils Wasserstoff, Hydroxyl- oder eine C_1-C_6-Alkoxy-Gruppe, X Cyano, Y -CO-NR^4R^5, worin R^4 und R^5 jeweils Wasserstoff, ein C_1-C_6-Alkyl oder eine Gruppe bedeuten, ausgewählt aus Benzyl, 2-Chlorbenzyl, 3-Chlorbenzyl, 4-Chlorbenzyl, 2-Methylbenzyl, 3-Methylbenzyl, 4-Methylbenzyl, 2-Methoxybenzyl, 3-Methoxybenzyl, 4-Methoxybenzyl, Phenethyl, 2-Picolyl, 3-Picolyl und 4-Picolyl; $-CH_2-NHSO_2-C_6H_5$ oder $-C(R^8)=NR^7$ sind, worin R^7 ein C_1-C_6-Alkoxy oder ein Aryl, R^8 -VR^9 sind, worin V Sauerstoff, Schwefel oder Stickstoff, R^9 ein Alkyl oder Aryl sind, oder ein pharmazeutisch akzeptables Salz davon.

8. Diphenylethylen-Derivat nach Anspruch 7, worin R^1 und R^2 jeweils C_1-C_6-Alkoxy-Gruppen sind, oder ein pharmazeutisch akzeptables Salz davon.

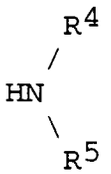
9. Diphenylethylen-Derivat nach Anspruch 8, worin R^1 und R^2 jeweils Methoxy-Gruppen sind oder ein pharmazeutisch akzeptables Salz davon.

10. Verfahren zur Herstellung eines Diphenylethylen-Derivates mit der allgemeinen Formel (I) nach Anspruch 7, worin R^1, R^2 und X wie oben definiert sind, Y -CO-NR^4R^5 ist, worin R^4 und R^5 jeweils wie oben definiert sind, oder eines pharmazeutisch akzeptablen Salzes davon, umfassend die Reaktion einer Carbonsäure der allgemeinen Formel (II):



(II)

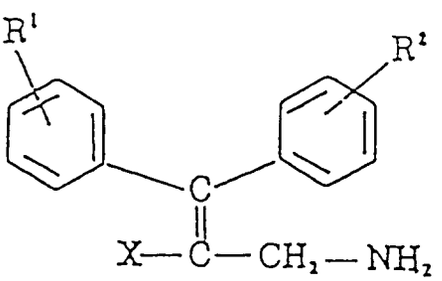
worin R^1, R^2 und X wie oben definiert sind, oder eines reaktiven Säure-Derivates davon mit einem Amin der allgemeinen Formel (III):



(III)

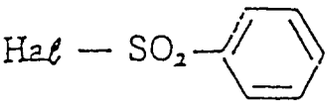
worin R^4 und R^5 wie oben definiert sind, und, falls erforderlich, Umwandlung des Produktes in ein pharmazeutisch akzeptables Salz.

11. Verfahren zur Herstellung eines Diphenylethylen-Derivates der allgemeinen Formel (I) nach Anspruch 7, worin R^1, R^2 und X wie oben definiert sind, Y -CH_2NHSO_2-C_6H_5 ist, oder eines pharmazeutisch akzeptablen Salzes davon, umfassend die Reaktion eines Amins der allgemeinen Formel (IV)



(IV)

worin R^1, R^2 und X wie oben definiert sind, mit einem Sulfonylhalogenid der allgemeinen Formel (V):



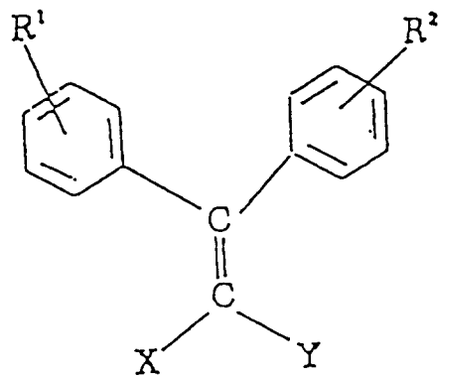
(V)

worin Hal ein Halogenatom bedeutet, und, falls erforderlich, Umwandlung der Produktes in ein pharmazeutisch akzeptables Salz.

12. Verfahren zur Herstellung eines Diphenylethylen-Derivates der allgemeinen Formel (I) nach Anspruch 7, worin R^1, R^2 und X wie oben definiert sind, Y -C(R^8)=NR^7 ist, worin R^7, R^8, V und R^9 wie oben definiert sind, oder eines pharmazeutisch akzeptablen Salzes davon, umfassend die Reaktion einer Verbindung der allgemeinen Formel (I) nach Anspruch 7, worin R^1, R^2 und X wie oben definiert sind, und Y -CONHR^7 ist, worin R^7 ein C_1-C_6-Alkoxy oder ein Aryl ist, mit einer Verbindung der Formel HVR^9, worin V und R^9 wie oben definiert sind, in der Gegenwart eines Halogenierungsmittels und, falls erforderlich, Umwandlung des Produktes in ein pharmazeutisch akzeptables Salz davon.

Patentansprüche für folgende Vertragsstaaten : AT, ES, GR

1. Verwendung eines Diphenylethylen-Derivates der Formel



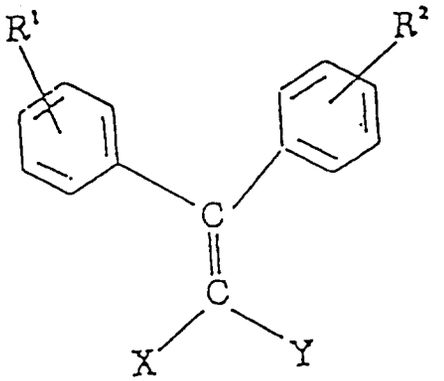
(I)

worin R^1 und R^2 unabhängig voneinander jeweils Wasserstoff, Hydroxyl- oder eine C_1-C_6-Alkoxy-Gruppe, X Cyano, Y -CO-NR^4R^5, worin R^4 und R^5 jeweils Wasserstoff, ein C_1-C_6-Alkyl oder eine Gruppe bedeuten, ausgewählt aus Benzyl, 2-Chlorbenzyl, 3-Chlorbenzyl, 4-Chlorbenzyl, 2-Methylbenzyl, 3-Methylbenzyl, 4-Methylbenzyl, 2-Methoxybenzyl, 3-Methoxybenzyl, 4-Methoxybenzyl, Phenethyl, 2-Picolyl, 3-Picolyl und 4-Picolyl; -CH_2-NHSO_2-C_6H_5 oder -C(R^8)=NR^7 sind, worin R^7 ein C_1-C_6-Alkoxy oder ein Aryl, R^8 -VR^9 sind, worin V Sauerstoff, Schwefel oder Stickstoff, R^9 ein Alkyl oder Aryl sind, oder eines pharmazeutisch akzeptablen Salzes davon zur Herstellung eines Medikamentes für die Behandlung von Erkrankungen, die durch Blutstromstörungen verursacht werden.

2. Verwendung nach Anspruch 1, worin in der Formel (I) R^1 und R^2 jeweils C_1-C_6-Alkoxy-Gruppen sind.

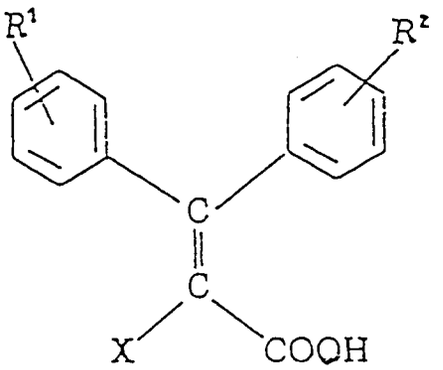
3. Verwendung nach Anspruch 2, worin der Formel (I) R^1 und R^2 Methoxy-Gruppen sind.

4. Verfahren zur Herstellung eines Diphenylethylen-Derivates mit der allgemeinen Formel (I)



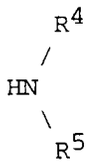
(I)

worin R^1 und R^2 unabhängig voneinander jeweils Wasserstoff, Hydroxyl- oder eine C_1-C_6-Alkoxy-Gruppe, X Cyano, Y -CO-NR^4R^5, worin R^4 und R^5 jeweils ausgewählt sind aus Benzyl, 2-Chlorbenzyl, 3-Chlorbenzyl, 4-Chlorbenzyl, 2-Methylbenzyl, 3-Methylbenzyl, 4-Methylbenzyl, 2-Methoxybenzyl, 3-Methoxybenzyl, 4-Methoxybenzyl, Phenethyl, 2-Picolyl, 3-Picolyl und 4-Picolyl, oder eines pharmazeutisch akzeptablen Salzes davon, umfassend die Reaktion einer Carbonsäure der allgemeinen Formel (II):



(II)

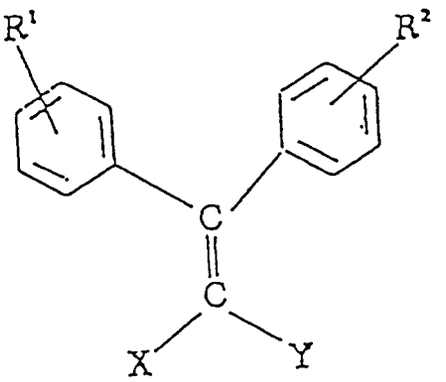
worin R^1, R^2 und X wie oben definiert sind, oder eines reaktiven Säure-Derivates davon mit einem Amin der allgemeinen Formel (III):



(III)

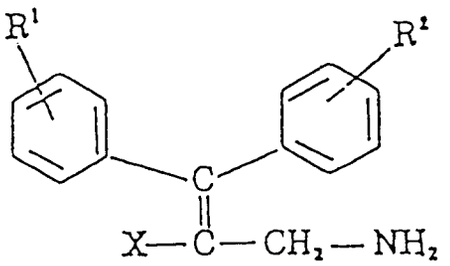
worin R^4 und R^5 wie oben definiert sind, und, falls erforderlich, Umwandlung des Produktes in ein pharmazeutisch akzeptables Salz.

5. Verfahren zur Herstellung eines Diphenylethylen-Derivates der Formel (I):



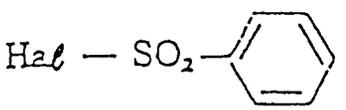
(I)

worin R^1 und R^2 jeweils unabhängig voneinander Wasserstoff, Hydroxyl oder eine C_1-C_6-Alkoxy-Gruppe, X Cyano, Y $-CH_2-NHSO_2-C_6H_5$ sind, oder eines pharmazeutisch akzeptablen Salzes davon, umfassend die Reaktion eines Amins der allgemeinen Formel (IV):



(IV)

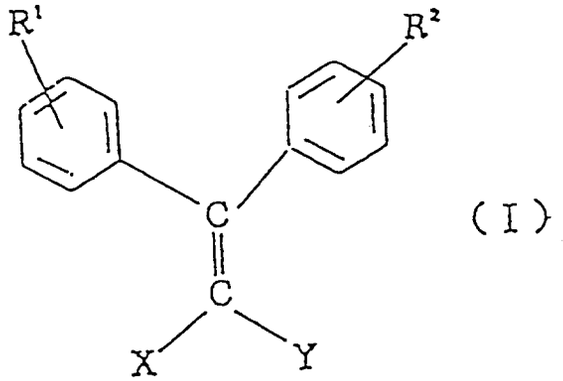
worin R^1, R^2 und X wie oben definiert sind, mit einem Sulfonylhalogenid der allgemeinen Formel (V):



(V)

worin Hal ein Halogenatom bedeutet, und, falls erforderlich, Umwandlung des Produktes in ein pharmazeutisch akzeptables Salz.

6. Verfahren zur Herstellung eines Diphenylethylen-Derivates der Formel (I):



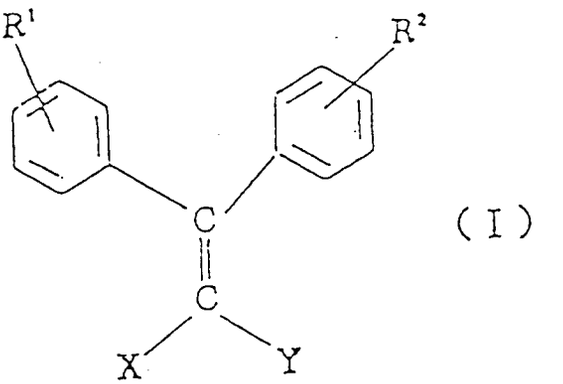
(I)

worin R^1 und R^2 jeweils unabhängig voneinander Wasserstoff, Hydroxyl oder eine C_1-C_6-Alkoxy-Gruppe, X Cyano, Y -C(R^8)=NR^7 sind, worin R^7 ein C_1-C_6-Alkoxy oder ein Aryl, R^8 -VR^9 sind, worin V Sauerstoff, Schwefel oder Stickstoff, R^9 ein Alkyl oder ein Aryl sind, oder eines pharmazeutisch akzeptablen Salzes davon, umfassend die Reaktion einer Verbindung der allgemeinen Formel (I) wie oben angegeben, worin R^1, R^2 und X wie oben definiert sind und Y -CONHR^7 ist, worin R^7 ein C_1-C_6-Alkoxy oder Aryl ist, mit einer Verbindung der Formel HVR^9, worin V und R^9 wie oben definiert sind, in der Gegenwart eines Halogenierungsmittels und, falls erforderlich, Umwandlung des Produktes in ein pharmazeutisch akzeptales Salz davon.

Revendications

Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composition pharmaceutique qui comprend une quantité pharmacologiquement efficace d'un dérivé de diphényléthylène de formule:



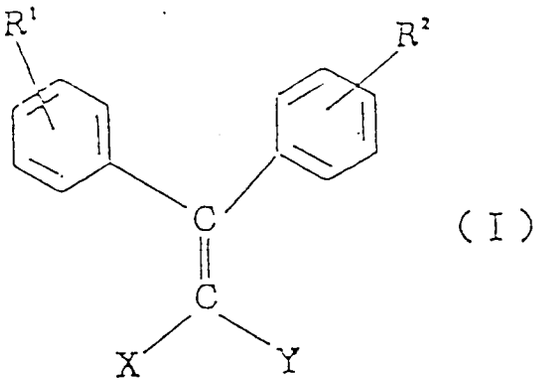
(I)

dans laquelle R^1 et R^2 sont, indépendamment l'un de l'autre, des atomes d'hydrogène ou des groupes hydroxyle ou alcoxy en C_1-C_6, X est un groupe cyano, Y est -CO-NR^4R^5, R^4 et R^5 étant chacun un atome d'hydrogène, un groupe alkyle en C_1-C_6 ou un groupe choisi parmi les groupes benzyle, 2-chlorobenzyle, 3-chlorobenzyle, 4-chlorobenzyle, 2-méthylbenzyle, 3-méthylbenzyle, 4-méthylbenzyle, 2-méthoxybenzyle, 3-méthoxybenzyle, 4-méthoxybenzyle, phénéthyle, 2-picolyle, 3-picolyle et 4-picolyle; -CH_2-NHSO_2-C_6H_5 ou -C(R^8)=NR^7, R^7 étant un groupe alcoxy en C_1-C_6 ou un groupe aryle, R^8 est -VR^9, V étant un atome d'oxygène, de soufre ou d'azote, R^9 étant un groupe alkyle ou un groupe aryle,
ou d'un sel pharmaceutiquement acceptable de ce composé,
et un véhicule pharmacologiquement acceptable.

2. Composition pharmaceutique selon la revendication 1, dans laquelle, dans la formule (I), les deux radicaux R^1 et R^2 sont des groupes alcoxy en C_1-C_6.

3. Composition pharmaceutique selon la revendication 2, dans laquelle, dans la formule (I), les deux radicaux R^1 et R^2 sont des groupes méthoxy.

4. Utilisation d'un dérivé diphényléthylène de formule:



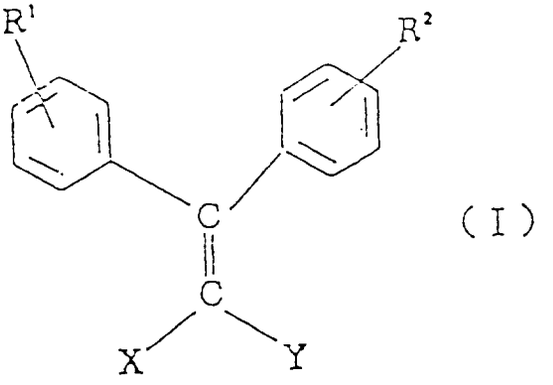
(I)

dans laquelle R^1 et R^2 sont, indépendamment l'un de l'autre, des atomes d'hydrogène ou des groupes hydroxyle ou alcoxy en C_1-C_6, X est un groupe cyano, Y est -CO-NR^4R^5, R^4 et R^5 étant chacun un atome d'hydrogène, un groupe alkyle en C_1-C_6 ou un groupe choisi parmi les groupes benzyle, 2-chlorobenzyle, 3-chlorobenzyle, 4-chlorobenzyle, 2-méthylbenzyle, 3-méthylbenzyle, 4-méthylbenzyle, 2-méthoxybenzyle, 3-méthoxybenzyle, 4-méthoxybenzyle, phénéthyle, 2-picolyle, 3-picolyle et 4-picolyle; -CH_2-$NHSO_2$-C_6H_5 ou -$C(R^8)$=NR^7, R^7 étant un groupe alcoxy en C_1-C_6 ou un groupe aryle, R^8 est -VR^9, V étant un atome d'oxygène, de soufre ou d'azote, R^9 étant un groupe alkyle ou un groupe aryle,
ou d'un sel pharmaceutiquement acceptable de celui-ci,
dans la préparation d'un médicament pour le traitement de maladies causées par des troubles de la circulation sanguine.

5. Utilisation selon la revendication 4, dans laquelle, dans la formule (I), les deux radicaux R^1 et R^2 sont des groupes alcoxy en C_1-C_6.

6. Utilisation selon la revendication 5, dans laquelle, dans la formule (I), les deux radicaux R^1 et R^2 sont des groupes méthoxy.

7. Dérivé de diphényléthylène de formule:



(I)

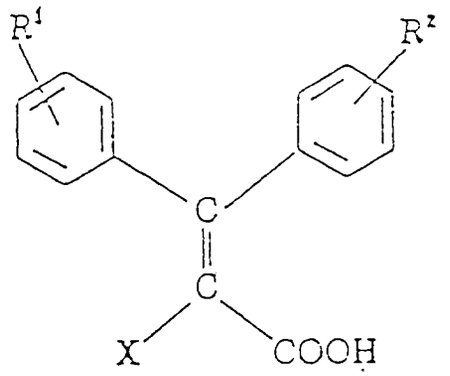
dans laquelle R^1 et R^2 sont, indépendamment l'un de l'autre, des atomes d'hydrogène ou des groupes hydroxyle

ou alcoxy en C_1-C_6, X est un groupe cyano, Y est -CO-NR^4R^5, R^4 et R^5 étant chacun un groupe choisi parmi les groupes benzyle, 2-chlorobenzyle, 3-chlorobenzyle, 4-chlorobenzyle, 2-méthylbenzyle, 3-méthylbenzyle, 4-méthylbenzyle, 2-méthoxybenzyle, 3-méthoxybenzyle, 4-méthoxybenzyle, phénéthyle, 2-picolyle, 3-picolyle et 4-picolyle; -CH_2-$NHSO_2$-C_6H_5 ou -$C(R^8)$=NR^7, R^7 étant un groupe alcoxy en C_1-C_6 ou un groupe aryle, R^8 est -VR^9, V étant un atome d'oxygène, de soufre ou d'azote, R^9 étant un groupe alkyle ou un groupe aryle,
ou un sel pharmaceutiquement acceptable de ce composé.

8. Dérivé de diphényléthylène selon la revendication 7, dans laquelle les deux radicaux R^1 et R^2 sont des groupes alcoxy en C_1-C_6, ou sel pharmaceutiquement acceptable de ce composé.

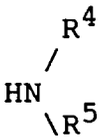
9. Dérivé de diphényléthylène selon la revendication 8, dans laquelle les deux radicaux R^1 et R^2 sont des groupes méthoxy, ou sel pharmaceutiquement acceptable de ce composé.

10. Procédé de préparation d'un dérivé de diphényléthylène de formule générale (I) indiqué dans la revendication 7, dans laquelle R^1, R^2 et X sont tels que définis ci-dessus, Y est -CO-NR^4R^5, R^4 et R^5 sont chacun tels que définis ci-dessus, ou d'un sel pharmaceutiquement acceptable de ce composé, qui comprend la réaction d'un acide carboxylique de formule générale (II):



(II)

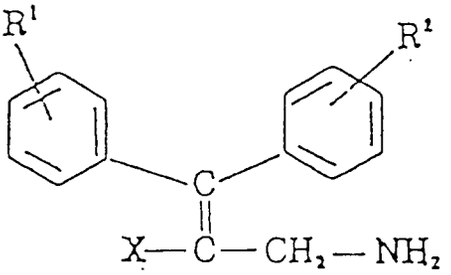
dans laquelle R^1, R^2 et X sont tels que définis ci-dessus, ou d'un dérivé acide réactif de celui-ci, avec une amine de formule générale (III):



(III)

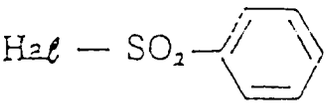
dans laquelle R^4 et R^5 sont tels que définis ci-dessus, et le cas échéant la conversion du composé en un sel pharmaceutiquement acceptable.

11. Procédé de préparation d'un dérivé de diphényléthylène de formule générale (I) indiqué dans la revendication 7, dans laquelle R^1, R^2 et X sont tels que définis ci-dessus, Y est un groupe -CH_2NHSO_2-C_6H_5, ou d'un sel pharmaceutiquement acceptable de ce composé, qui comprend la réaction d'une amine de formule générale (IV):



(IV)

dans laquelle R^1, R^2 et X sont tels que définis ci-dessus, avec un halogénure de sulfonyle de formule générale (V):



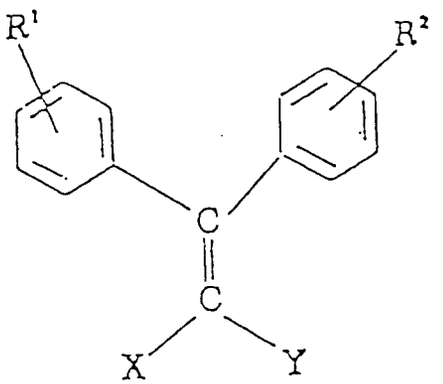
(V)

dans laquelle Hal représente un atome d'halogène, et le cas échéant la conversion du produit en un sel pharmaceutiquement acceptable.

12. Procédé de préparation d'un dérivé de diphényléthylène de formule générale (I) indiqué dans la revendication 7, dans laquelle R^1, R^2 et X sont tels que définis ci-dessus, Y est $-C(R^8)=NR^7$, R^7, R^8, V et R^9 étant tels que définis ci-dessus, ou d'un sel pharmaceutiquement acceptable de ce composé, qui comprend la réaction d'un composé de formule générale (I) indiqué dans la revendication 7, dans laquelle R^1, R^2 et X sont tels que définis ci-dessus et Y est $-CONHR^7$, R^7 étant un groupe alcoxy en C_1-C_6 ou un groupe aryle, avec un composé de formule HVR^9, dans laquelle V et R^9 sont tels que définis ci-dessus, en présence d'un agent d'halogénation, et le cas échéant la conversion du produit en un sel pharmaceutiquement acceptable de ce composé.

Revendications pour les Etats contractants suivants : AT, ES, GR

1. Utilisation d'un dérivé de diphényléthylène de formule:



(I)

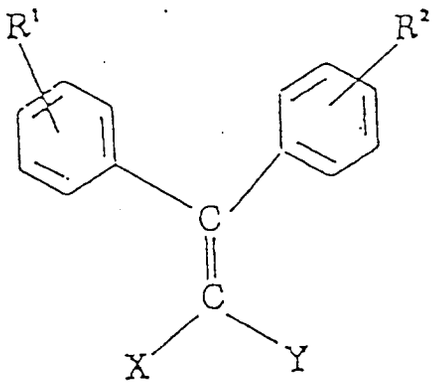
dans laquelle R^1 et R^2 sont, indépendamment l'un de l'autre, des atomes d'hydrogène ou des groupes hydroxyle ou alcoxy en C_1-C_6, X est un groupe cyano, Y est $-CO-NR^4R^5$, R^4 et R^5 étant chacun un atome d'hydrogène, un groupe alkyle en C_1-C_6 ou un groupe choisi parmi les groupes benzyle, 2-chlorobenzyle, 3-chlorobenzyle, 4-chlorobenzyle, 2-méthylbenzyle, 3-méthylbenzyle, 4-méthylbenzyle, 2-méthoxybenzyle, 3-méthoxybenzyle, 4-méthoxybenzyle, phénéthyle, 2-picolyle, 3-picolyle et 4-picolyle; $-CH_2-NHSO_2-C_6H_5$ ou $-C(R^8)=NR^7$, R^7 étant un groupe alcoxy en C_1-C_6 ou un groupe aryle, R^8 est $-VR^9$, V étant un atome d'oxygène, de soufre ou d'azote, R^9 étant un

groupe alkyle ou un groupe aryle,
ou d'un sel pharmaceutiquement acceptable de ce composé,
dans la préparation d'un médicament pour le traitement des maladies causées par les troubles de la circulation sanguine.

2. Utilisation selon la revendication 1, dans laquelle, dans la formule (I), les deux radicaux R^1 et R^2 sont des groupes alcoxy en C_1-C_6.

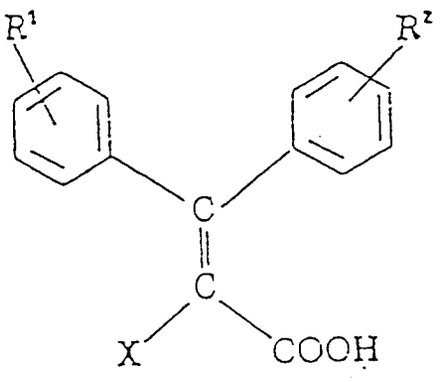
3. Utilisation selon la revendication 2, dans laquelle, dans la formule (I), les deux radicaux R^1 et R^2 sont des groupes méthoxy.

4. Procédé de préparation d'un dérivé diphényléthylène de formule (I):



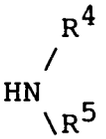
(I)

dans laquelle R^1 et R^2 sont, indépendamment l'un de l'autre, des atomes d'hydrogène ou des groupes hydroxyle ou alcoxy en C_1-C_6, X est un groupe cyano, Y est -CO-NR^4R^5, R^4 et R^5 étant chacun un groupe choisi parmi les groupes benzyle, 2-chlorobenzyle, 3-chlorobenzyle, 4-chlorobenzyle, 2-méthylbenzyle, 3-méthylbenzyle, 4-méthylbenzyle, 2-méthoxybenzyle, 3-méthoxybenzyle, 4-méthoxybenzyle, phénéthyle, 2-picolyle, 3-picolyle et 4-picolyle; ou d'un sel pharmaceutiquement acceptable de ce composé, qui comprend la réaction d'un acide carboxylique de formule générale (II):



(II)

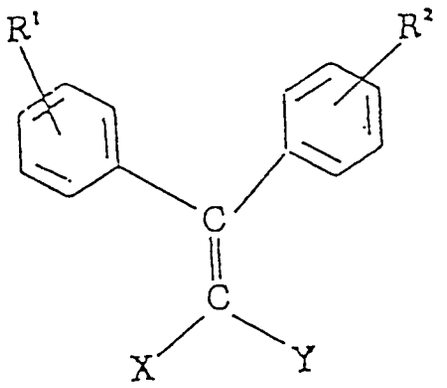
dans laquelle R^1, R^2 et X sont tels que définis ci-dessus, ou d'un dérivé acide réactif de celui-ci, avec une amine de formule générale (III):



(III)

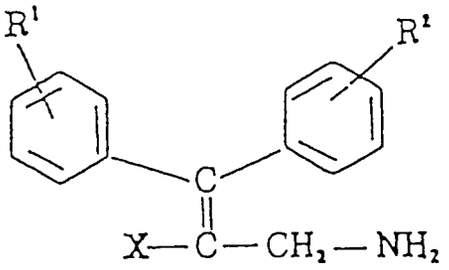
dans laquelle R^4 et R^5 sont tels que définis ci-dessus, et le cas échéant la conversion du composé en un sel pharmaceutiquement acceptable.

5. Procédé de préparation d'un dérivé de diphényléthylène de formule (I):



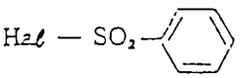
(I)

dans laquelle R^1 et R^2 sont, indépendamment l'un de l'autre, des atomes d'hydrogène ou des groupes hydroxyle ou alcoxy en C_1-C_6, X est un groupe cyano, Y est un groupe CH_2NHSO_2-C_6H_5, ou d'un sel pharmaceutiquement acceptable de ce composé, qui comprend la réaction d'une amine de formule générale (IV):



(IV)

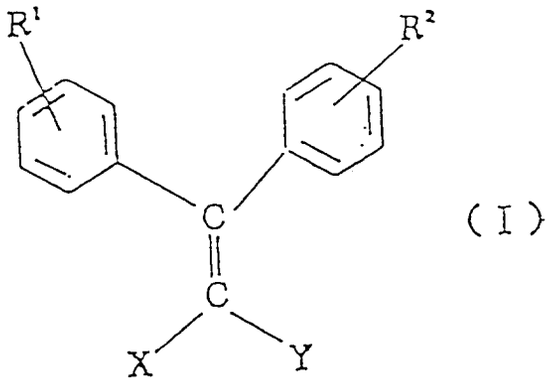
dans laquelle R^1, R^2 et X sont tels que définis ci-dessus, avec un halogénure de sulfonyle de formule générale (V):



(V)

dans laquelle Hal représente un atome d'halogène, et le cas échéant la conversion du produit en un sel pharmaceutiquement acceptable.

6. Procédé de préparation d'un dérivé de diphényléthylène de formule (I):



(I)

dans laquelle R^1 et R^2 sont, indépendamment l'un de l'autre, des atomes d'hydrogène ou des groupes hydroxyle ou alcoxy en C_1-C_6, X est un groupe cyano, Y est $-C(R^8)=NR^7$, R^7 étant un groupe alcoxy en C_1-C_6 ou un groupe aryle, R^8 est $-VR^9$, V étant un atome d'oxygène, de soufre ou d'azote, R^9 étant un groupe alkyle ou un groupe aryle, ou d'un sel pharmaceutiquement acceptable de ce composé, qui comprend la réaction d'un composé de formule générale (I) indiqué ci-dessus, dans laquelle R^1, R^2 et X sont tels que définis ci-dessus et Y est $-CONHR^7$, R^7 étant un groupe alcoxy en C_1-C_6 ou un groupe aryle, avec un composé de formule HVR^9, dans laquelle V et R^9 sont tels que définis ci-dessus, en présence d'un agent d'halogénation, et le cas échéant la conversion du produit en un sel pharmaceutiquement acceptable de ce composé.